REMARKS

Claims 1, 3, 5, 7, 10-11 and 44-49 were pending in this application. Applicants have by this Amendment canceled claims 1, 3, 5, 7, and 10-11 without prejudice, amended claim 44, and added new claims 50-56. Thus, claims 44-56 are currently pending in the subject application.

Applicants have canceled the claims solely to expedite the prosecution of the subject application. Applicants, however, do not relinquish their right to claim or otherwise pursue patent coverage for the canceled or deleted subject matter.

Rejection under 35 U.S.C. § 112, first paragraph - enablement

On pages 2-9 of the June 4, 2002 Office Action, the Examiner rejected claims 1, 3, 5, 7, 10-11 and 44-49 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the previous Office Action.

The Examiner acknowledged that the specification teaches by exemplification that using the yeast two hybrid assay, two clones encoding a portion of a protein were selected from a library of human liver Matchmaker cDNA for interacting with a portion of hepatitis C virus E2 lacking its most hydorphobic, carboxyl terminal domain. The sequence of the encoded portion of a protein, referred to as E_0 protein, has the amino acid sequence of SEQ ID NO: 1. Furthermore, the specification teaches that the encoded amino acid sequence containing amino acid residues 1-120 of SEQ ID NO:1 (or $E_0$1 protein) is also

capable of binding to the portion of hepatitis C virus E2 as does the E_0 protein of SEQ ID NO:1, although at a relatively weaker binding affinity (See specification, pages 18-20).

However, the Examiner alleged that the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to methods of treating or preventing hepatitis C virus infection or preventing attachment of hepatitis C virus onto a cell in a subject using an effective amount of E_0 protein having amino acids 1-120 of SEQ ID NO: 1. The Examiner then asserted that the instant specification is not enabled for the clinical invention.

In response, applicants have canceled method of treatment claims 1, 3, 5, 7, 10 and 11 to expedite prosecution of the subject application.

With respect to applicants' claims directed to the method of inhibiting attachment of HVC to cells, applicants understand the Examiner to be raising two issues. First, the Examiner noted that Rosa et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS) have reported that in contrast to E2 protein expressed in mammalian cells, E2 protein expressed in yeast or insect cells are not capable of binding to human cells (see Fig. 1), nor do they elicit neutralizing antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate (page 1761, col. 2, top of first full paragraph). Thus, the Examiner found unclear the significance of the interaction between E_0 or E_01 protein with a portion of a hepatitis C virus E2 envelope protein solely in yeasts as reported in this application.

Second, the Examiner alleged that there is also no evidence of record (*in vitro* or *in vivo*) indicating that the E_0 protein of the present invention can disrupt the E1 and E2 heteromeric complex (already formed complex) that is thought to be necessary for HCV virus binding and entry to the cells as taught by Yi et al. and asserted by Applicants. The Examiner took the position that the endogenous E1/E2 heteromeric complex is already present in the HCV virus. As such, the Examiner questioned how can a simple application of Eo protein of the instant invention disrupt the E1/E2 heteromeric complex to prevent HCV attachment.

In response to the first point, applicants point out that Rosa et al. modified a yeast strain to first express the full length E2 protein in the yeast, and then to secrete the full length protein. Then, Rosa et al. purified the secreted E2 protein. Of note is that Rosa et al. performed all of these steps differently between their mammalian and yeast expressed E2.

Applicants on the other hand expressed only a 384-661 a.a. fragment of the full length E2 protein (see page 18, lines 15-17 of the specification). Applicants also did not modify the yeast to secrete the protein. Also, applicants did not purify the protein. Applicants avoided steps which could have modified the protein.

Cocquerel et al., J.Virol 1998 Mar;72(3):2183-91, attached as **Exhibit 1**, offer an explanation for the apparent difference noted by Rosa et al. Rosa et al. expressed the full length sequence of E2 which included the transmembrane domain, which includes an endoplasmic reticulum retention signal. However,

Rosa et al. in its second paragraph of the Material and Methods section clearly stated that E2 was "secreted" from CHO cells, and also secreted form yeast cells. To have its full length E2 with the retention signal secreted, Rosa et al. must have done something which also modified the E2 binding activity in the yeast system.

Furthermore, Cocquerel et al. clearly confirm that "only a shorter secreted form of E2 glycoprotein ending at amino acid 661 appears to be properly folded." Page 2183, right column, lines 4-6 of Cocquerel et al. Applicants' data is based on such a shorter E2, whereas the data of Rosa et al. is not.

Moreover, Heile et al., J.Virol 2000 Aug;74(16):6885-92, copy attached as **Exhibit 2**, have shown that complex-glycosylated secreted fraction of E2 expressed even in mammalian cells do not bind to human cells. It is thus entirely likely that the different purification used by Rosa et al. between the mammalian expressed E2 and the yeast expressed E2 resulted in differences in glycosylation of their E2. Applicants' data, on the other hand, was not subject to such difficulty.

Due to the lower amount of processing, and particularly due to the absence of purification, it is reasonable to expect applicants' truncated E2 protein to more closely resemble the E2 protein on HCV.

With respect to the Examiner's second concern, applicants point out that the "formation of stable E1-E2 complexes is slow (half time of association ($t_{1/2}$ ~ 2h)." Page 2183, left column, lines 14-16 of Cocquerel et al. Thus, an agent has sufficient time to interfere in this complex formation.

However, interruption of this complex formation does not appear to be necessary for inhibition of binding of E2 to a cell. Cocquerel et al. teaches that the point of binding between E1 and E2 is the same retention sequence referenced above. Applicants' binding data is based on E2 without this retention sequence. Thus, applicants' binding data is independent of whether the E2 is alone or in complex with E1.

Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

New claims

Applicants have also added new claims 50-56 which applicants submit are not subject to the rejections set forth in the June 4, 2002 Office Action.

No fee, other than the enclosed $55.00 for the one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Washington, D.C. 20231.

Gary J. Gershik 10/4/02
Gary J. Gershik Date
Reg. No. 39,992

Claims with Revision Shown

44. (Amended) A method of ~~preventing~~ inhibiting attachment of hepatitis C virus onto a cell, which comprises contacting the cell with an effective amount of an Eo protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the Eo protein is capable of inhibiting the attachment of hepatitis C virus onto the cell by specifically binding to the hepatitis C virus envelope E2 protein.

45. The method of claim 44, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:2.

46. The method of claim 44, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:3.

47. The method of claim 44, wherein the Eo protein comprises amino acids having the amino acid sequence shown in SEQ ID NO:1

48. The method of claim 44, wherein the cell is a liver cell.

49. The method of claim 48, wherein the liver cell is a human liver cell.

50. (New) A method of modifying the activity of the hepatitis C virus envelope E2 protein, which comprises contacting the E2 protein with an Eo protein having amino acids 1-120 of SEQ ID NO:1.

51. (New) The method of claim 50, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:2.

52. (New) The method of claim 50, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:3.

53. (New) The method of claim 50, wherein the Eo protein comprises amino acids having the amino acid sequence shown in SEQ ID NO:1.

54. (New) The method of claim 50, wherein the cell is a liver cell.

55. (New) The method of claim 54, wherein the liver cell is a human liver cell.

56. (New) An isolated complex between the hepatitis C virus envelope E2 protein and an Eo protein having amino acids 1-120 of SEQ ID NO:1.